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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,824	05/23/2001	C. Alexander Turner JR.	LEX-0181-USA	8987

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	17

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/863,824	TURNER ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 5/9/2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *07 March 2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☒ Applicant's reply has overcome the following rejection(s): see attached.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *see attached*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *none*.

   Claim(s) objected to: *none*.

   Claim(s) rejected: *2,3,6 and 7*.

   Claim(s) withdrawn from consideration: *none*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☒ Other: *PTO-892*

ADVISORY ACTION

1. Claims 2-3 and 6-7 are pending.

2. The request for entering amendments to claim 2, cancellation of non-elected claims 4-5, and arguments filed on 5/9/2003 under 37 CFR 1.116 in reply to the Final Action Paper No. 13 mailed on 12/3/2002 are acknowledged. The proposed amendments to the claims will be entered since they are deemed sufficient to overcome the 35 USC 112, second paragraph rejection previously applied to claim 2 and simplify the issues for appeal. However, entry of these amendments is not deemed sufficient to place the application in condition for allowance for the following reasons.

3. Claims 2-3 and 6-7 have been rejected under 35 USC 101 because the claimed invention is not supported by either a substantial and specific asserted utility or a well established utility. The instant claims have also been rejected under 35 USC, first paragraph since the one of skill in the art would not know how to use the claimed invention since the invention is not supported by a specific, substantial and credible utility or a well established utility.

4. Applicants argue that the claimed polynucleotides have a number of substantial and credible utilities, in particular those related to polymorphisms as indicated in the specification at page 16, lines 21-31. Applicants submit that the Final Action discounts Applicant's assertion regarding the use of the claimed polynucleotides on DNA chips and that the polymorphisms described have specific utility in DNA gene chip analysis. Furthermore, Applicants argue that the claimed polynucleotides provide a specific marker of the human genome and that these specific markers are targets for drug discovery. In addition, Applicants argue that the present

polynucleotides have specific utility in determining the genomic structure of the corresponding human chromosome, specifically in the localization of the specific region of the human chromosome containing the gene encoding the given polynucleotide, which is a utility not shared by other polynucleotides.

Applicants further submit that the claimed polynucleotides provide biologically-validated empirical data that specifically define that portion of the corresponding genomic locus that actually encodes an exon. As such, Applicants argue that the claimed polynucleotides have utility since one of skill in the art can understand the relevance of expressed, spliced, and polyadenylated mRNA. Applicants submit Exhibit C as evidence to support Applicant's contention that the claimed polynucleotides can be used in localizing the specific region of the human chromosome and can be used to identify functionally active intron/exon splice junctions. According to Applicants, Exhibit C shows that the polynucleotide of the present invention contains more than 7 exons which spread non-contiguously along a region of human chromosome 20, at approximately 20q12, and conclude that one could not identify these exons without knowing the polynucleotides of the claimed invention.

Finally, Applicants submit that the Examiner is holding Applicant's invention to a different legal standard of patentability and that it is unclear as to how their invention, which is free of prior art and fully disclosed, could retain less utility and be less enabled than other inventions cited in US patents which were filed when the level of skill in the art was lower. It is Applicant's contention that the USPTO does not have the authority to write US law and that is should administer US law in an unbiased and procedurally consistent manner.

5. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejections. The polynucleotide of SEQ ID NO: 1 and its corresponding polypeptide (SEQ ID NO: 2) were found to lack utility since the specification fails to disclose a substantial, specific or well established utility. As indicated in previous Office Actions, while the specification has suggested that the polypeptide of SEQ ID NO: 2 is a thrombospondin polypeptide, the art teaches that the closest structural homolog is a serine palmitoyltransferase having 36.8% sequence identity to the polypeptide of SEQ ID NO: 2 and the closest structural homolog with the claimed function (thrombospondin) is only 5% sequence identical to the polypeptide of SEQ ID NO: 2. The specification provides no empirical evidence of its biological function. Thrombospondins belong to a family of at least 5 members in vertebrates, each with diverse functions. Therefore, even if the claimed polynucleotides encode a thrombospondin, the claimed polynucleotides lack specific utility since there is no disclosure in the specification of the type of thrombospondin encoded by the polynucleotide of SEQ ID NO:1.

The state of the art clearly teaches the unpredictability of assigning function based on structural homology and discloses several examples of how even small structural changes can lead to major changes in function. Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* where found to be hydroxylases once tested for activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring

Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Therefore, in view of the fact that the closest structural homologs of the claimed invention encode proteins of different functions and the teachings of the art in regard to annotating function based on structural homology, the instant polynucleotides have no substantial utility since in order to identify or reasonably confirm a "real world" context of use, one of skill in the art would have to further conduct additional research.

While it is acknowledged that the specification at page 16, lines 21-32 indicates that polymorphisms can exist a positions 364, 365 and 535 of SEQ ID NO: 1, there is no disclosure as to what is the biological significance of these polymorphisms. As such, the use of these polynucleotides to detect such polymorphisms in a DNA chip is not a specific and substantial utility since detection of these polymorphisms using DNA chips is meaningless unless one can link the presence or absence of such polymorphisms to some biological function. Similarly, it is unclear as to how one can use the claimed polynucleotides as specific markers which can be used to discover drugs that are associated with human disease if (1) the diseases associated with said polynucleotides are unknown, (2) there is no information as to whether it is the expression of the polynucleotide, or lack thereof, which correlates with disease, (3) there is no information as to whether the presence of the polymorphisms of SEQ ID NO: 1 as indicated above correlate with any disease, and (4) no information in regard to the correlation between levels of expression of the claimed polynucleotides and disease has been presented.

In regard to arguments that the claimed polynucleotides have specific utility since they can be used to detect the genomic structure of the corresponding human chromosome or to detect the location of the instant polynucleotides within said chromosome, it is noted that any polynucleotide which is complementary to any of the genes in that chromosome can be used as a marker for that particular chromosome. In addition, while it is agreed that the claimed polynucleotides can be used to detect the specific locus which contains the corresponding gene, any polynucleotide encoding a gene product can be used to identify its corresponding locus.

In regard to arguments that the present invention introduces biologically validated empirical data, it is noted that no experimental evidence could be found in the specification which shows that the polynucleotide of SEQ ID NO: 1 is indeed an mRNA transcript. Therefore, there is no assurance that the assembled cDNA of SEQ ID NO: 1, which encodes the polypeptide of SEQ ID NO: 2, is indeed an actual transcript of a gene since it is known in the art that computer-based assembly of genes and their transcripts (cDNA) is not perfect and may lead to wrong splicing of genes. Since Applicants provide no experimental evidence to corroborate that the claimed polynucleotides are indeed the actual transcripts of a gene, one cannot reasonably conclude that the claimed polynucleotides provide biologically validated data.

The Examiner acknowledges Applicant's submission of Exhibit C, however as indicated above, in view of the lack of experimental data demonstrating that the polynucleotide of SEQ ID NO: 1 is indeed the actual transcript of a gene, and in the absence of data in the prior art which would corroborate Applicant's assertion in regard to the number and/or location of exons in the claimed polynucleotide, it is unclear as to how one can use the claimed invention to specifically detect functionally active intron/exon splice junctions.

The Examiner disagrees with Applicant's contention that their invention is being held to a different legal standard of patentability. The Examiner has examined the instant application according to the guidelines set forth by the USPTO as well as the MPEP, which are believed to be consistent with US law. While it is agreed that the claimed polynucleotides are free of the prior art and their structure is disclosed (i.e. sequence), it is noted that the instant claims are being rejected due to lack of utility and not because there is prior art or because the structure is not disclosed. In regard to the patentability of other US patents, Applicants are reminded that each application is examined on its own merits according to the current guidelines of examination as set forth by the USPTO and a discussion on the utility of any polynucleotide claimed in such patents would require a detailed review of the record of each individual case, which would be improper herein. Finally, Applicants are reminded that the Examiner has no authority to comment in regard to how the USPTO administers US law.

6. The 35 USC 101 and 112, first paragraph rejections previously applied are, therefore, maintained for the reasons of record and the reasons set forth above.

7. For purposes of Appeal, the status of the claims is as follows:

Claim(s) allowed: NONE

Claims(s) objected to: NONE

Claim(s) rejected: 2-3 and 6-7

Claim(s) withdrawn from consideration: NONE

8. Applicants are requested to submit a clean copy of the pending claims (including amendments, if any) in future written communications to aid in the examination of this application.

9. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
May 29, 2003

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1300~~ 1600